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Chronic Traumatic Encephalopathy: Where Are We and Where Are We Going?

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Abstract Chronic traumatic encephalopathy (CTE, previously called punch drunk and dementia pugilistica) has a rich history in the medical literature in association with boxing, but has only recently been recognized with other contact sports, such as football and ice hockey, as well as with military blast injuries. CTE is thought to be a neurodegenerative disease associated with repeated concussive and subconcussive blows to the head. There is characteristic gross and microscopic pathology found in the brain, including frontal and temporal atrophy, axonal degeneration, and hyperphosphorylated tau and TAR DNA-binding protein 43 pathology. Clinically, there are characteristic progressive deficits in cognition (memory, executive dysfunction), behavior (explosivity, aggression), mood (depression, suicidality), and motor function (parkinsonism), which correlate with the anatomic distribution of brain pathology. While CTE shares clinical and neuropathological traits with other neurodegenerative diseases, the clinical syndrome and the neuropathology as a whole are distinct from other neurodegenerative diseases. Here we review the CTE literature to date. We also draw on the literature from mild traumatic brain injury and other neurodegenerative dementias, particularly when these studies provide guidance for future CTE research. We conclude by suggesting seven essential areas for future CTE research.

Keywords Chronic traumatic encephalopathy (CTE) · Dementia pugilistica · Traumatic brain injury (TBI) · Concussion · Tauopathy · Neurofibrillary tangle · TDP-43 · Apolipoprotein E (APOE E)

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Introduction

In 1928, Martland wrote that "[i]t is easily conceivable…that, after many cranial injuries unassociated with fracture of the skull…a progressive degenerative lesion may be the late manifestation". He presented a series of boxers who later in life developed a "parkinsonian syndrome [and]… marked mental deterioration … necessitating commitment to an asylum". He called this condition "punch-drunk" [1•]. In 1934, Parker presented several more cases from the Mayo Clinic in a paper entitled "Traumatic encephalopathy ('punch drunk') of professional pugilists", and, in 1937, Millspaugh coined the term "dementia pugilistica" [2, 3]. Although isolated cases continued to appear in the medical literature, it was not until 1973 when Corsellis et al. [4•] published their landmark series of 15 cases describing the clinical and pathological features, that dementia pugilistica was differentiated from other neurodegenerative diseases. The term chronic traumatic encephalopathy (CTE) is now used more widely to acknowledge that the pathology can occur in a wider population than just boxers [5–7].

Clinical and pathological criteria for CTE have been proposed by various authors [8•, 9–11], although no currently

validated consensus criteria exist. Broadly, CTE is considered to be a neurodegenerative disease associated with repeated concussive and subconcussive blows to the head. There is characteristic gross and microscopic brain pathology, and progressive deficits in cognition, behavior, mood, and motor function.

Although there is evidence for an association between history of repeated concussive or subconcussive injuries, and chronic cognitive and behavioral impairment [7, 8••, 12•], there are insufficient data to confirm a causal link. No epidemiological, cross-sectional, or prospective studies of CTE currently exist [13]. However, wild-type mice exhibit neuropathology in some ways analogous to CTE 2 weeks after a controlled blast-exposure and behavioral and motor deterioration after repetitive concussive injury [14•, 15]. Additionally, human tau transgenic mice demonstrate increased tau immunoreactivity after repetitive impact injury [16].

Historically, the terms concussion and mild traumatic brain injury (mTBI) have been used interchangeably. Concussion is defined by the American Academy of Neurology as a clinical syndrome of biomechanically induced alteration of brain function, typically affecting memory and orientation, which may involve loss of consciousness [17]. Subconcussion refers to head trauma that does not rise to the level of concussion, i.e., is asymptomatic. Post-concussion syndrome (PCS) refers to a constellation of physical, cognitive, and behavioral symptoms that persist in a small number of concussion patients. There are several formal definitions (International Statistical Classification of Diseases and Related Health Problems 10th Revision and Diagnostic and Statistical Manual of Mental Disorders DSM-IV-TR Fourth Edition [18, 19]) that remain controversial. The proposed minimum time that symptoms must persist varies from 1 week to 3 months [20]. Although all reported cases with CTE pathology have had a history of repetitive blows to the head, not all cases had a documented history of concussion, raising the suspicion that individuals with subconcussive injuries may also be susceptible to CTE [7], [8•, 21]. CTE is clinically distinct from the immediate sequelae from a head injury including PCS, and, in most cases, the symptoms of CTE begin long after the occurrence of trauma (usually 8–10 years) [7, 8•, 9]. Nonetheless, because there is symptomatic overlap between PCS and CTE, and because symptoms of PCS can be quite prolonged, clinical distinction can sometimes be challenging [22].

Clinical Presentation

CTE deficits can be in cognition, behavior, mood, or motor function. Based on patient and informant interview, as well as on neurological examination, the most prominent early cognitive deficits tend to be in memory and executive function. Over half of pathologically confirmed cases have memory symptoms. Similarly to Alzheimer's disease (AD), patients have difficulty remembering recently formed memories, but have preserved distant memories. In addition, patients commonly have difficulty with concentration, judgment, and problem-solving. While patients also have language and visuospatial deficits, these tend to occur later in the disease course [7, 8•, 9, 12•, 23–26].

The most prominent early behavioral deficits tend to be explosivity and aggression. Additional deficits in behavior can include poor impulse control, paranoid ideations, poor insight, disinhibition, risky behavior, inappropriate sexual behavior, deterioration of interpersonal and intrafamily relationships, verbal and physical abuse, and substance abuse. Owing to both cognitive (problem-solving difficulty) and behavioral (risky behavior) deficits, patients may have difficulty managing money and investments, at times leading to bankruptcy [5–7, 8•, 9, 24–26]. The most prominent early mood deficits tend to be depression and hopelessness. Additional deficits in mood can include suicidality, anxiety, agitation, apathy, and, rarely, mania [5–7, 8•, 9, 24–26].

Additional signs and symptoms include headache, parkinsonism (including tremor, decreased facial expression, rigidity, and gait instability), dysarthria, dysphagia, coordination difficulty, and gaze disturbances. Headache tends to be an early complaint, while the other signs and symptoms tend to occur in more advanced disease [6, 7, 8•, 9, 23, 26]. In addition, a subset of patients has motor neuron disease (MND, termed chronic traumatic encephalomyelopathy). Signs and symptoms include weakness, muscle atrophy, spasticity, and fasciculations. The shoulder girdles, neck, arms, and bulbar musculature are typically involved. MND tends to be the initial presentation in these patients with cognitive, behavioral, and mood deficits occurring later [8•, 27••].

Typically, age of symptom onset of CTE is between 30 and 65 years, though pathologic evidence has been found as early as age 14 years. Earlier case reports of boxers suggested that there may be two distinct clinical presentations of CTE: an earlier presentation of mood and behavior change, and a later presentation of cognitive impairment, including dementia [4•, 28]. Our group recently published the largest case series of neuropathologically confirmed CTE in athletes without other comorbidities. Based on retrospective interviews with family members of the deceased athletes, our results supported the previous findings of two clinical presentations. The group that presented with mood and behavioral changes had a mean age of presentation of 34.5 years, while the group that presented with cognitive impairment had a mean age of presentation of 58.5 years [26]. Based on pathological data, the rate of decline tends to be slower than in AD or frontotemporal dementia (FTD), with progression at a rate of 11–14 years between pathological stages [8•]. As in most degenerative forms of dementia, there is severe global impairment in advanced disease. Without knowledge of the earlier clinical picture, it is hard to distinguish advanced CTE from other causes of dementia [26, 29].

There are no clinical consensus criteria for CTE. Jordan [10, 11] has proposed clinical criteria for boxers and, more

recently, has suggested that these criteria are broadly applicable. According to his criteria, "probable" CTE must have two or more of the following conditions: 1) cognitive and/or behavioral impairment; 2) cerebellar dysfunction; 3) pyramidal tract disease or extrapyramidal disease. The presentation must be consistent with the clinical description of CTE and clinically distinguishable from other disease processes. "Possible" CTE must be consistent with the clinical description of CTE, but could be explained by another disease process. "Improbable" CTE is inconsistent with the clinical description of CTE and can be explained by another disease process that is unrelated to brain trauma [10, 11]. These criteria have not been validated or widely cited. While these criteria are useful, there are inherent flaws: there is no discussion of head injury, such as the severity, the minimum number of events, or the temporal relationship to the neurologic deficits. Additionally, there is no mention of meeting criteria for dementia or alternatively of demonstrating neurologic decline. Also, it is unclear if having motor dysfunction (pyramidal or extrapyramidal disease) or cerebellar dysfunction should be a necessary requirement for probable CTE. Our group found that only 20 % of cases with pathologically proven CTE had these deficits (though this finding was based on retrospective informant interview rather than neurologic examination). Cerebellar pathology at autopsy was sparse and only found in the most severely affected cases [8•]. Lastly, including a statement about consistency with the clinical description in clinical criteria is inherently circular. Plans to compose and validate clinical consensus criteria are currently underway.

While CTE has clinical characteristics of other degenerative diseases, the combination of signs and symptoms together may uniquely distinguish it. The prominent poor impulse control, executive dysfunction, and early age of onset of CTE are reminiscent of behavioral variant FTD (bvFTD). Further, MND is associated with both CTE and bvFTD [30]. However, our recent work suggests that disinhibition and inappropriateness, which are very common in bvFTD, are less common in CTE [26, 31]. Also, bvFTD lacks the memory impairment characteristic of CTE. While the prominent memory impairment of CTE is similar to AD, mild AD patients typically do not have prominent behavioral symptoms. The combination of dementia and parkinsonism periodically seen in CTE may resemble dementia with Lewy bodies (DLB). However, parkinsonism tends to be a late feature of CTE and explosivity and aggression are atypical of DLB [32].

Neuropathology

Our group and others have shown that CTE is a pathologically distinct tauopathy that can be clearly differentiated from other neurodegenerative diseases, including AD and FTLD [4•, 5–7, 8•, 9, 14•, 27••, 33–35]. These differences are present at both the gross and microscopic levels.

Gross Pathology

In mild CTE, gross examination reveals subtle changes including enlargement of the lateral and third ventricles, and, occasionally, pallor of the locus coeruleus and substantia nigra. In more advanced disease, there is reduced brain weight, frontal and temporal atrophy with prominent medial temporal atrophy with compensatory dilation of the lateral and third ventricles. There is also atrophy of the thalamus, hypothalamus, and mammillary body, thinning of the corpus callosum, and reduction in subcortical white matter. Frequently, there is a cavum septum pellucidum or septal fenestrations. These septal abnormalities are most likely acquired as a result of trauma-induced fluid waves in the ventricles that over time injure the septum pellucidum and are more likely a marker of head trauma than an independent risk factor for CTE [4•, 7–9].

Microscopic Pathology

On the microscopic level, neurofibrillary tangle (NFT) pathology—intracellular aggregates of phosphorylated tau protein—are the hallmark of CTE. Inclusions form in both neurons and glial cells. As in AD, all six tau isoforms are found in the NFTs [36]. However, unlike in AD, NFTs in CTE are irregularly/unevenly distributed with a tendency to form around blood vessels and at the depths of the sulci, especially in early stages of the disease. When NFTs are diffusely distributed, they are preferentially found in the superficial layers of cerebral cortex. Neurofibrillary pathology tends to be particularly prominent in the frontal and temporal lobes, and ultimately densely involves hippocampus, amygdala and entorhinal cortex. Other areas of dense NFTs include the olfactory bulb, diencephalon, substantia nigra, locus coeruleus, and cerebellar dentate nucleus. In areas of dense pathology, the NFT density may be greater than that found in other tauopathies [5, 7, 8•, 9, 14•, 33–35, 37–39].

Axonal injury is also present in all cases of CTE. In mild disease, axonal pathology is limited to multifocal axonal varicosities in frontal and temporal cortex, subcortical white matter, and deep white matter tracts. In more advance disease, axonal loss is diffuse, affecting the subcortical white matter and white matter tracts. In advanced disease, neuronal loss is prominent, particularly in the hippocampus, entorhinal cortex, and amygdala, and, to a lesser extent, in the locus coeruleus, substantia nigra, and medial thalamus [7, 8•].

TAR DNA-binding protein 43 (TDP-43) neuronal and glial inclusions are also found in the majority of CTE cases (> 80 % in our brain bank), most commonly in association with severe tau pathology. Inclusions have been found throughout the cortex and subcortical white matter, including the frontal, medial temporal (including the hippocampus and amygdala) and insular cortices, basal ganglia (including caudate and

putamen), thalamus, hypothalamus, and brainstem (including substantia nigra pars compacta) [8•, 27••, 34].

Unlike AD, amyloid beta (Aβ) deposition is not a universal pathologic feature of CTE. Multiple authors have noted the relative predominance of diffuse Aβ plaques in CTE compared with neuritic Aβ plaques, a necessary hallmark of AD [4•, 9, 37–39]. In our case series, Aβ deposition (either as diffuse plaques, neuritic plaques, or vascular amyloid) was present in 44 % of CTE cases and was significantly associated with age. Ten percent of CTE cases also met pathologic criteria for AD. Thirty-seven percent had comorbid neurodegenerative disease including AD, MND, Parkinson's disease (PD), DLB, and frontotemporal lobar degeneration [8•]. Head trauma is a well-established epidemiological risk factor for AD and has also been associated with MND and PD [40–43]. It is possible that repetitive mTBI and axonal injury could activate multiple molecular pathways involved in the inappropriate aggregation of proteins common to neurodegenerative diseases.

While there are no pathological consensus criteria for CTE, both Omalu et al. [9] and our group have proposed various criteria. Omalu et al. [9] defined four distinct phenotypes based on the type and anatomic distribution of histopathology (Table 1). Our group has employed four criteria necessary to define pathological CTE (termed here McKee criteria; Table 2). We have also defined four stages of severity based on the extent of phosphorylated tau (p-tau) pathology (termed here McKee stages; Table 3).

Clinicopathologic Correlation

Although detailed quantitative pathological analysis and clinical correlation has not been performed, the general anatomic distribution of tau pathology correlates with the cognitive, behavioral, mood, and motor symptoms most frequently seen in CTE. As in AD, the accumulation of NFTs in the hippocampus, entorhinal cortex, and parahippocampal gyrus likely leads to the memory deficits. Involvement of the superior, dorsolateral, and lateral frontal cortices may account for the apathy and executive dysfunction, and involvement of the orbitofrontal cortices and inferior temporal cortices (including the amygdala) may produce explosive outbursts and poor impulse control. Involvement of the basal ganglia and substantia nigra probably leads to the gait instability and parkinsonism. It is unknown if the anatomic distribution of tau pathology differs by age as the distinct age-associated clinical presentations may suggest.

In mTBI, rapid head acceleration leads to stretching of white matter axons, resulting in diffuse axonal injury. Injury leads to disruption in axonal transport, axonal swelling, and, ultimately, Wallerian degeneration. Axonopathy can continue for years after the head injury [44]. While the connection between repetitive mild TBI and progressive neurodegeneration is not well understood, it is possible that early symptoms of CTE, like headache and concentration difficulty, might be due to axonal injury given the small amount of tau pathology early in the disease [8•].

Table 1 Chronic traumatic encephalopathy pathological phenotypes as defined by Omalu et al. [9]

1	Cerebral cortex: sparse to frequent NFTs and NTs Brainstem: sparse to frequent NFTs and NTs Subcortical nuclei/basal ganglia: present or absent NFTs and NTs Diffuse amyloid plaques: absent
2	Cerebral cortex: sparse to frequent NFTs and NTs Brainstem: sparse to frequent NFTs and NTs Subcortical nuclei/basal ganglia: present or absent NFTs and NTs Diffuse amyloid plaques: sparse to frequent
3	Cerebral cortex: absent or sparse NFTs and NTs Brainstem: moderate to frequent NFTs and NTs Subcortical nuclei/basal ganglia: absent to sparse NFTs and NTs Diffuse amyloid plaques: absent
4	Cerebral cortex: absent to sparse NFTs and NTs Brainstem: absent to sparse NFTs and NTs Subcortical nuclei/basal ganglia: absent to sparse NFTs and NTs Diffuse amyloid plaques: absent

NFTs neurofibrillary tandles, *NTs* XXX

Phenotypes are defined by the type and anatomic distribution of histopathology

Epidemiology

There is very limited epidemiological data on CTE because there have been no cross-sectional or prospective studies. Because CTE was historically a disease of boxers, older studies focused exclusively on them. A prevalence study limited to former professional boxers from 1969 showed that 17 % had neurologic deficits reasonably attributable to boxing. Risk factors included retirement after the age of 28 years, boxing longer than 10 years, and engaging in 150 or more fights [24]. Other studies of boxers have implicated increasing sparring exposure and history of a technical knockout or knockout [45, 46]. The number of fights of a typical

Table 2 Chronic traumatic encephalopathy (CTE) pathological criteria as defined by McKee et al. [8••]

1	Perivascular foci of p-tau immunoreactive astrocytic and NFTs
2	Irregular cortical distribution of p-tau immunoreactive astrocytic and NFTs with predilection for the depths of cerebral sulci
3	Clusters of subpial and periventricular astrocytic tangles in the cerebral cortex, diencephalon, basal ganglia, and brainstem
4	NFTs in the cerebral cortex located preferentially in the superficial layers

p-Tau phosphorylated tau, *NFTs* neurofibrillary tanges

All four criteria must be met to have pathological CTE

Table 3 Chronic traumatic encephalopathy pathological stages as defined by McKee et al. [8••]

1	Discrete foci in the cerebral cortex, normally surrounding small vessels at the depths of sulci, largely limited to frontal lobes, usually the superior, dorsolateral or lateral cortices
2	Multiple epicenters at the depths of the cerebral sulci with localized spread from these epicenters to the superficial layers of adjacent cortex, more extensive involvement of the frontal lobes, as well as anterior, inferior, and lateral temporal cortices, inferior parietal, insular, and septal cortices with sparing of the medial temporal cortices
3	Widespread involvement, still most pronounced in the depths of the sulci, most prominent in the frontal and temporal lobes, though also involving the insular and parietal cortices, the amygdala, the hippocampus, the entorhinal cortex
4	Diffuse, severe pathology throughout the cerebral cortex and the medial temporal structures, usually spares the calcarine cortex

Stages are based on extent and anatomic distribution of phosphorylated-tau pathology

professional boxer has declined substantially since 1969, which may have an impact on the prevalence [47].

More recently, pathological evidence of CTE has been found in a variety of contact sports and other activities in which head trauma occurs. It has been pathologically verified in athletes from the following sports: boxing, American football, wrestling, soccer, hockey, and rugby [5–7, 8•, 37]. It has also been pathologically confirmed in soldiers who have experienced multiple blast injuries [8•]. In addition, it has been found in patients with epilepsy, patients with autism (from head banging), abuse victims, and a circus clown recurrently shot from a cannon [7, 33, 38].

The relationship between CTE and exposure to concussions and subconcussions is incompletely understood, but likely crucially important. In American football players with pathologically confirmed CTE, the stage of p-tau pathology (a measure of severity) was associated with years played and thus indirectly with the amount of head trauma [8•]. There are no data on the minimum threshold of head injuries required to develop CTE, though a study of professional American football players showed that players with a history of at least three concussions were five times more likely to report being diagnosed with mild cognitive impairment, three times more likely to have memory complaints, and three times more likely to report being diagnosed with depression compared with those without a history of concussion [12•, 48]. Another study of professional American football players demonstrated that player neurodegenerative mortality was three times higher than that of the general US population and that "speed player" (non-lineman and non-kickers) neurodegenerative mortality was three times higher than that of "non-speed players" (lineman). The authors hypothesized that the higher momentum blows that speed players endure might be responsible for this difference [49•]. Interestingly, a review of 36 observational studies of amateur boxers (who have far fewer fights and wear head gear) did not demonstrate an association between amateur boxing and chronic traumatic brain injury, though the quality of the studies was judged to be poor [50]. Similarly, in a community-based study of individuals who were high school students in Rochester, Minnesota, between 1946 and 1956, high school football players had no increased risk of dementia, PD, or MND compared with non-football-playing classmates [51].

Although, there are scant epidemiological data on CTE, there are far more epidemiological data on mTBI. While mTBI data certainly cannot be extrapolated to CTE, it might, nonetheless, offer some insight into CTE. mTBI has large public health implications. The US annual incidence of mTBI is 1.2 million, and the estimated annual number of outpatient and emergency department visits for mTBI in the USA exceeds 2 million. Eighty percent of all TBI is mild [52, 53]. Five to 20 % with mTBI develop PCS [20, 54]. Athletes with a concussion history have a 5.8-times greater risk of a subsequent concussion, and there is a suggestion that there is a dose–response relationship between the number of previously sustained concussions and the risk for future concussion [55, 56]. Together, these statistics suggest that CTE could have a significant impact on public health.

There is ongoing debate regarding whether age at time of head injury affects recovery. Some researchers have hypothesized that immature brains are more plastic and thus better able to recover from concussion [57], while others have argued that a developing brain is more susceptible to injury [58]. Compared with younger children, adolescents are more likely to develop PCS after mTBI [59]. However, compared with college athletes who suffered concussion, high school athletes who suffered concussion had prolonged memory dysfunction [60]. Interestingly, on MR spectroscopy, while adults have changes in N-acetyl aspartate (NAA) concentrations after mild TBI, children do not [61, 62]. Whether age at the time of head injuries affects risk of development of CTE is an open question and an active area of investigation.

Gender may also play a role in recovery from concussion. Female athletes have greater concussion rates, report greater increases in symptoms after concussion, and have greater impairment on neuropsychological testing after concussion compared with male athletes. It is unclear if these differences are biomechanical, hormonal and/or are due to reporting bias [63–66]. In CTE, the vast majority of patients studied have been men because brain donation has largely occurred among professional athletes in contact sports.

Genetics

All cases of neuropathologically confirmed CTE have had a history of repetitive mTBI. However, not all individuals with

exposure to these injuries go on to develop CTE. This suggests that repetitive mTBI is necessary, but not sufficient for the development of CTE. Therefore, it is critical to examine additional potential risk factors, including genetic risk factors, for the pathogenesis of this disease. The notion that dementia is associated with a gene-environment interaction between head trauma and the presence of genetic risk factors dates back to 1995. Mayeux et al. [67] initially found that head trauma was associated with incidence of AD only in the presence of an *APOEε4* allele. While this finding has been difficult to replicate [68, 69], there is a clearer association between *APOEε4* and an unfavorable outcome following recurrent mTBI. Among current and former boxers, *APOEε4* carriers were more impaired on a global scale quantifying motor, cognitive, and psychiatric deficits [70]. Among 53 active American professional football players, older players who were *APOEε4* carriers were more impaired on measures of global cognition, processing speed, and attention [71]. In human *APOE* transgenic mice that underwent mild-to-moderate head injury, *APOEε4* carriers had different microarray expression patterns in the hippocampus and cortex compared with non-carriers [72]. Recent work suggests that *APOE* is expressed in neurons in response to neuronal damage (e.g., from head injury). In neurons, the apoE protein conformation makes it susceptible to proteolytic cleavage. The resulting cleavage fragment has been shown to be neurotoxic [73]. The role of *APOE* in CTE remains ambiguous. In 68 pathologically proven cases of CTE from our center, the frequency of *APOEε4* carriers did not differ from the frequency in the US population [8•]. However, we have shown that in a subset of these cases (plus several new cases), all of whom were athletes who had no comorbid neurodegenerative or MND, *APOEε4* homozygotes were over-represented compared with the general population [26]. In all likelihood, *APOE* will only explain a fraction (if any) of the heritability of CTE. Genome-wide family-based and case–control genetic studies will likely be required to explain the genetic architecture of CTE.

Like other neurodegenerative diseases, the only way to make a definitive CTE diagnosis is pathologically. In other neurodegenerative diseases, the use of neuropsychological testing, imaging, and cerebrospinal fluid (CSF) biomarkers has allowed clinicians to diagnose these conditions in life with more confidence. A similar approach to CTE is conceivable, though its development is in its infancy.

Neuropsychological Testing

Because nearly all CTE studies have been retrospective autopsy studies, patient performance on neuropsychological tests has hardly been examined. These studies are currently underway. Unlike CTE, there is substantial data on neuropsychological performance following mTBI. As with the epidemiological data on mTBI, the neuropsychology of mTBI cannot be simply extrapolated to CTE, but, nonetheless, may offer some insight. A meta-analysis of eight studies of healthy former athletes showed that compared with a history of only one mTBI, a history of repeated mTBI was associated with reduced delayed recall and executive function, but not with impairment in attention or language. A small, non-significant effect was seen for visuospatial function. Participants in these studies had suffered their concussions at least 4 months prior to neuropsychological testing [74•]. There is also evidence that subconcussive blows to the head can affect neuropsychological performance. High school football players who sustained head injuries that did not result in any reported symptoms still had lower scores in visual working memory (as well as decreased activation in the dorsolateral frontal cortex on fMRI) on post-season evaluation compared with pre-season evaluation. Not surprisingly, these asymptomatic players did not undergo a clinical assessment during the game and continued to play [75•]. Hart et al. [76•] recently studied 34 retired professional American football players (age range, 47–71 years), all but two of whom had suffered at least one concussion (range, 0–13) and about half of whom had cognitive impairment (at least some of which was presumably due to CTE). They found that the cognitively impaired players had deficits in naming, word finding, and visual and verbal episodic memory [76•]. Larger replication cohorts will be required to confirm these findings.

Imaging

As with the other clinical sections of this review, there are far more imaging studies of mTBI than there are of CTE. While not a substitute for CTE studies, mTBI imaging studies do offer some guidance for evaluating patients with suspected CTE. Here we discuss chronic findings associated with mTBI for a range of imaging modalities, and whether these modalities might be applied to CTE.

Computed Tomography

Computed tomography (CT) is a widely available and frequently used technique to evaluate structural pathology in the brain. Because it depicts anatomy in less detail than structural magnetic resonance imaging (MRI), it is less commonly used in dementia research. Nonetheless, a study from 1983 showed that in former boxers the number of bouts was associated with the amount of global atrophy on CT [77]. In clinical evaluation of CTE, CT would probably be used when patients have a contraindication to MRI.

MRI

In mTBI, longitudinal studies using volumetric MRI demonstrated a greater decrease in global atrophy over time. Regional analyses showed differences in the cingulate and precuneus white and gray matter [78–80]. These studies and the focal and global atrophy present on neuropathological evaluation of CTE brains suggest that structural MRI may be a valuable diagnostic technique for CTE as it is for other forms of dementia.

Susceptibility weighted imaging (SWI) is an MRI sequence that accentuates the paramagnetic properties of blood products rendering it very sensitive for detecting microhemorrhages in head trauma from diffuse axonal injury [81]. While microhemorrhages on SWI are commonly found in moderate and severe TBI, they are less commonly found in mTBI [79]. Further, boxers and former professional American football players have not been found to have significantly more microhemorrhages than the general population [76•, 82, 83]. However, a Korean study found that compared with controls, microhemorrhages were more commonly found in those with mTBI, were in a different anatomic distribution (white matter rather than deep nuclei), and portended a worse prognosis 1 year after the event [84]. There have been no published studies in CTE. We suspect that while white matter microhemorrhages on SWI may offer additional confirmation that an impaired patient suffered axonal injury, they are unlikely to be a sensitive or specific marker for CTE.

MRI diffusion tensor imaging (DTI) can produce detailed white matter tract images using measurement of water molecule diffusion within white matter. Several measures of this diffusion, including fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AXD) and radial diffusivity (RD), are markers of white matter integrity [85]. In a meta-analysis of 13 DTI studies of mTBI, FA was reduced and MD was increased in the corpus callosum compared with controls. Unfortunately, the time between trauma and the scan differed from 3 days to 8 years [86] . Longitudinal analyses have been inconsistent regarding whether these DTI changes resolve over time [87–89], though increased MD in multiple brain regions has been associated with poorer outcome after 3–4 months [90]. Increases in AXD and RD have been found cross-sectionally in professional soccer players compared with competitive swimmers, and longitudinally over the course of a season in university hockey players [91, 92•]. Further, in the study by Hart et al. [76•], retired professional American football players with cognitive deficits had reduced FA in frontal, parietal, and temporal regions, as well as the corpus callosum, compared with controls and with players without cognitive deficits. Given that axonal injury might be the early trigger for later degeneration, MRI DTI may play an important role in diagnosis of CTE. However, before this is possible, future DTI studies will need to show whether white matter damage resulting from CTE can be differentiated from white matter damage resulting from trauma itself. Additionally, because there are also DTI changes in AD [93], future studies will not just need to show whether DTI can differentiate CTE cases from controls, but also whether it can differentiate CTE cases from AD cases.

There are two types of functional MRI (fMRI) methods that may be useful in CTE: blood oxygenation level dependent (BOLD) and arterial spin labeling (ASL) imaging. Both can measure brain function either in the resting state or as the patient performs a task. In BOLD fMRI imaging, brain function is measured by changes in the oxygenation of blood hemoglobin [94]. In a meta-analysis of 14 BOLD fMRI studies of mTBI with imaging performed 6.5 days to 6.4 months after the event, BOLD hyperactivation, especially of the dorsolateral prefrontal cortex, was associated with continuous tasks of working memory in cases compared with controls. Interestingly, BOLD hypoactivation in the same region was associated with discrete tasks of working memory in cases compared with controls [95]. While there have been fewer BOLD fMRI resting state studies, they tend to consistently show decreased connectivity in the posterior cingulate cortex and increased connectivity in the prefrontal cortex acutely. These changes resolve over 4 months [96–98]. ASL uses magnetically labeled water molecules as an endogenous tracer for measuring brain perfusion. While BOLD is susceptible to baseline drift over time and possesses significant inter-subject variability, this is not the case for ASL [99], potentially making it a better method for measuring brain function in CTE. In the study by Hart et al. [76•], retired professional American football players with cognitive deficits had variation in regional blood flow in the left temporal pole, inferior parietal lobule, and superior temporal gyrus on ASL compared with controls [76•]. As in other forms of dementia, fMRI for CTE will likely be an important tool for research, though its role in clinical practice is still unclear.

Magnetic resonance spectroscopy (MRS) can reliably detect multiple neurometabolites that appear as a spectrum of peaks at specific frequencies. The height of the peak represents the concentration of the metabolite in the brain [100]. Multiple MRS longitudinal studies of mTBI demonstrated changes in NAA (a marker of viable neurons), creatine (a reference for the evaluation of other peaks) and Glx (a measure of combined glutamate and glutamine and a marker for excitotoxicity) in the frontal white matter compared with controls acutely. However, all levels eventually returned to baseline by 1–5 months [61, 101–103]. Interestingly, one of the studies showed that individuals who had a second head injury took 15 days longer to recover [101]. Importantly, another showed increased myo-inositol (a marker of membrane injury) only after 6 months, suggesting it could be indicative of chronic injury [102]. One pilot study has used MRS to compare former professional athletes who had a history of multiple concussions and symptoms concerning for CTE to healthy,

age-matched controls. Compared with controls, cases showed increased choline (another marker of membrane injury) and increased Glx [100]. Given these findings, MRS could be an important adjunct to both structural and function imaging in CTE.

Single Photon Emission Computed Tomography

Single photon emission CT (SPECT) characterizes regional cerebral blood flow by collecting data from an infused gamma-emitting isotope [104]. Acutely, patients with mTBI show decreased perfusion in the frontal lobes [105]. Many studies have used SPECT to evaluate mTBI chronically (1 month to 12 years post-injury). In a comprehensive review of these studies, Lin et al. [100] state that the preponderance of regions with hypoperfusion were in the frontal and parietal lobes, though hypoperfusion was also noted in the basal ganglia, the occipital lobes, the parietal lobes, and the cerebellum. Compared with controls, 100 active and former American football players (age range 25–82 years), whose cognition spanned from normal to demented and who reported 0 to > 5 episodes of LOC, demonstrated decreased perfusion in the prefrontal poles, temporal poles, occipital lobes, cingulate gyrus, and hippocampus [106]. Lack of SPECT findings probably portends a good prognosis. A longitudinal evaluation of mTBI patients demonstrated that SPECT abnormalities had high sensitivity and high negative predictive value for any clinical symptoms up to a year after the trauma [107]. SPECT is already widely used clinically for differentiating dementia types. Studies are needed to show whether SPECT can differentiate CTE from AD or FTD, though the aforementioned studies are certainly promising.

Positron Emission Tomography

Like SPECT, positron emission tomography (PET) detects an infused biologically-active radiolabeled tracer. Several tracers exist and can be used to detect various physiologic and pathophysiologic processes. Fludeoxyglucose (FDG), an analogue of glucose, is rapidly taken up by brain cells and is a marker of metabolic activity [108]. Nearly all FDG–PET studies that evaluated mTBI were conducted in the chronic setting (months to years after the trauma) and have been inconsistent [100]. For instance, two recent studies evaluated patients with a history of multiple concussions, but found differing results. Provenzano et al. [109] found that current boxers had reduced FDG uptake in the frontal, parietal and occipital lobes, cingulate gyrus, and cerebellum compared with controls. However, Peskind et al. [110] found that former soldiers (mean age 32±8.5 years) who had experienced multiple blast exposures (range, 3–51) that met criteria for mTBI had reduced FDG uptake in the cerebellum, pons, and medial temporal lobes. The different findings in these studies might reflect differences in the type of head injuries obtained (boxing versus blast injury).

As NFTs are a hallmark of CTE pathology, tau pathology is an obvious target for a PET tracer. Tau-specific radioligands have been developed and preliminarily used in PET imaging of patients with AD and MCI, as well as in normal controls [111]. FDDNP, a PET ligand that non-selectively binds both NFT and amyloid plaque deposition, was recently used in a preliminary study of five retired American professional football players (aged 45–73 years) with mood and cognitive symptoms. Compared with controls, there were higher signals in all subcortical regions and the amygdala [112]. Tau imaging will likely be of immense utility in CTE. Future studies using tau-specific tracers (rather than tracers such as FDDNP that non-selectively bind both tau and amyloid pathology) in larger cohorts of retired athletes who have suffered head injuries will be crucial.

CSF and Blood Biomarkers

The CSF is a sensible source for biomarkers in neurodegenerative disease because it directly baths the brain and its biochemical composition may therefore reflect underlying brain pathology. Because CSF biomarkers have been successfully developed and are regularly used in the clinical diagnosis of AD, they serve as a model for CTE. As is the case for the other clinical sections in this review, studies in mTBI have been conducted, but are lacking/ongoing for CTE. Two studies of amateur boxers evaluated several CSF proteins shortly after a bout (1–10 days) and after a delay (2 weeks–3 months). Compared with controls, one of the studies found elevated total-tau acutely, but levels returned to normal after the delay. p-Tau, the most established CSF biomarker to date for NFT pathology (at least in AD), was not elevated. More promising, both studies found neurofilament light polypeptide, a prominent component of the neuronal cytoskeleton, especially in large-caliber myelinated axons, to be elevated immediately and after the delay compared with controls [113, 114].

While serum biomarkers are more desirable than CSF biomarkers because their attainment is less invasive, effective assays are more difficult to develop because the blood–brain barrier impedes central nervous system (CNS) protein diffusion into the plasma. Proteins that make it to the plasma are further diluted by the plasma's large volume making them even more difficult to detect [115]. Glial fibrillary acidic protein, a CNS-specific intermediate filament protein that is a well-known target for pathological staining, was found to be elevated acutely in plasma in mTBI patients with abnormal imaging findings (suggesting their injuries may, in fact, have been more severe). It was not predictive of outcome [116]. As in the CSF, elevated plasma tau levels have been detected in boxers acutely after a bout, but levels significantly decreased

after a 2-week delay [117]. As with imaging studies, fluid biomarkers will only prove truly useful if protein levels can differentiate neurodegeneration resulting from CTE from brain injury resulting from trauma itself.

Conclusions and Future Directions

As noted throughout this review, CTE research is just beginning. Nonetheless, over the last few years, the topic has achieved public prominence owing to the sizeable place contact sports have in our society, as well as the large number of head injuries recently sustained by soldiers fighting in Iraq and Afghanistan. Research on other neurodegenerative diseases provides an excellent model for how we should go about studying CTE: 1) prospective, longitudinal epidemiological studies to determine the incidence and prevalence of CTE in the general population and to analyze whether a causal link exists between head injury and CTE; 2) careful clinical phenotyping in order to develop clinical consensus criteria; 3) studies of clinicopathological correlation in order to develop pathological consensus criteria; 4) identification of biomarkers, including structural, functional, and tau radioligand imaging, and CSF and serum protein levels to aid in early diagnosis; 5) identification of CTE risk factors, including specific aspects of TBI exposure (number of injuries, age at injury, injury severity, etc.) and non-TBI factors; 6) family-based and case–control genetic studies to better understand the genetic architecture of CTE, especially the gene-environment interaction; 7) in conjunction with the study of other tauopathies, translational studies into the prevention of tau aggregation, and propagation.

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Compliance with Ethics Guidelines

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Recently published papers of particular interest have been highlighted as:
- • Of importance
- •• Of major importance

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